Remarks

Reconsideration of this Application is respectfully requested.

I. Status Of The Claims

Claims 1, 3, 4, 9, 12, 56, 57-60 and 64 have been amended herein.

Claims 2, 5-8, 10, 11, 13-49 are canceled without prejudice to or disclaimer of the subject matter therein.

New claims 71-75 have been added.

Pending claims 1 and 9 are independent claims, and pending claims 3, 4, 12 and 50-75 are dependent claims.

Support for amended claims 1 and 9 can be found in the specification as filed, for example, at page 30, lines 9-21; and page 18, lines 2-5.

Support for the amendment of claim 56 is found in the Specification, for example, at page 36, line 12.

Claim 57 has been amended to correct the claim dependency.

Support for amended claims 60 and 64 is found in the Specification, for example, at page 14, lines 7-9.

New dependent claims 71-75 have been added. These claims depend from independent claim 9 and are similar to previously presented dependent claims 55-59 (which depend from independent claim 1). Support for these claims can be found in the Specification, for example, at page 29, line 27 to page 30, line 2; and page 36, lines 10-34.

No new matter has been added by these amendments.

II. Summary Of Examiner Interview

On June 1, 2011, the undersigned and Dr. Doyle Siever, who is in-house patent counsel at Intrexon Corporation, the assignee of the present application, met with Examiner Shafer and Examiner Stucker. The outstanding indefiniteness and written description rejections were discussed. Applicants and the undersigned thank the Examiners for the courteous and frank discussion.

III. The Objection To Claim 56

At page 2 of the Office Action, the Examiner objected to claim 56, because in lines 4-5, no species of ecdysone receptor ligand binding domain is recited. Claim 56 has been amended herein to recite "Orthopteran" ecdysone receptor ligand binding domain.

IV. The Obviousness Type Double-Patenting Rejection

At page 3 of the Office Action, the Examiner rejected claims 1-4, 7, 50-52, 55 and 56 for obviousness type double-patenting over claims 1, 3, 4 and 21-36 of U.S. Application No. 12/707,599. Applicants request that this rejection be held in abeyance until otherwise allowable subject matter has been identified. Applicants also reserve the right to argue that if a terminal disclaimer is ultimately filed, that it be filed in U.S. Application No. 12/707,599, not in the present application.

V. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

At page 4 of the Office Action, the Examiner rejected claims 1-4, 7, 9, 10, 12 and 50-54 under 35 U.S.C. § 112, second paragraph, for indefiniteness. Applicants respectfully traverse this rejection.

With regard to independent claim 1, the Examiner stated:

> It is unclear if Applicants intend a ***single polynucleotide*** to encode a single chimeric polypeptide comprising a DNA binding domain, an ecdysone receptor ligand binding domain, a second nuclear receptor ligand binding domain and a transactivation domain or ***a first polynucleotide*** encoding a polypeptide comprising a DNA binding domain and an ecdysone receptor ligand binding domain and ***a second polynucleotide*** encoding a second polypeptide comprising a nuclear receptor ligand binding domain capable of forming a dimer with the ecdysone receptor ligand binding domain and a transactivation domain or ***a first polynucleotide*** encoding a polypeptide comprising a DNA binding domain, an ecdysone receptor ligand binding domain and a second nuclear receptor ligand binding domain and ***a second polynucleotide*** encoding a polypeptide encoding a transactivation domain or something else entirely.

Office Action at pages 4-5 (emphasis in original).

At page 5 of the Office Action, the Examiner made a similar statement about claim 2, section (b). Claim 2 has been canceled.

With regard to independent claim 9, the Examiner stated:

> It is unclear if the receptor complex comprises ***a single polypeptide*** comprising a DNA binding domain, an ecdysone receptor ligand binding domain, a nuclear receptor ligand binding [domain] and a transactivation domain or ***a first polypeptide*** comprising a DNA binding domain and an ecdysone receptor ligand binding domain and ***a second polypeptide*** comprising a second nuclear receptor ligand binding domain and a transactivation domain or some other combination of polypeptides.

Office Action at page 6 (emphasis in original).

The Examiner also stated:

> [T]he only working examples are directed to polynucleotides encoding polypeptides comprising a DNA binding domain, and an ecdysone ligand binding domain and polynucleotides encoding polypeptides comprising a

> transactivation domain and a chimeric RXR-USP ligand binding domain. There are no examples, working or prophetic, of polynucleotides encoding, for example, chimeric polypeptides comprising an ecdysone ligand binding domain and a second ligand binding domain.

Office Action at page 7.

The Examiner also stated,

> The fact that there are two, plausible alternative interpretations of the independent claims of the instant invention render the claims indefinite. It is suggested that Applicants amend the claims to clearly recite the claimed alternatives.

Office Action at page 8.

At page 26 of the specification, at line 27, Applicant disclosed that an individually operable gene regulation system can comprise *one or more* polynucleotides encoding the components of a receptor complex (the DNA binding domain, the ligand binding domain, *etc.*). Hence, in view of the present specification, one of ordinary skill in the art would have understood that the components of the receptor complex can be encoded by one polynucleotide or by more than one polynucleotide.

At page 8 of the Office Action, the Examiner objected to claim 2 for lack of antecedent basis. Claim 2 has been canceled.

At page 8 of the Office Action, the Examiner objected to the dependency of claim 57, because claim 57 depends from canceled claim 22. Claim 57 has been amended herein to depend from claim 56.

Applicants respectfully request that this rejection be reconsidered and withdrawn.

VI. The Rejection Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

At page 8 of the Office Action, the Examiner rejected claims 1-4, 7, 9, 10, 12 and 50-70 under 35 U.S.C. § 112, first paragraph, for lack of written description. Applicants respectfully traverse this rejection.

At pages 9-10 of the Office Action, the Examiner explained that independent claim 1 had been interpreted to read on a single polynucleotide encoding a receptor complex, and that independent claim 9 had been interpreted to read on a gene regulation system comprising a single polypeptide. At page 10 of the Office Action, the Examiner explained that claim 1 is "drawn to a genus, i.e., a ***single polynucleotide*** encoding a receptor complex . . . ," and that claim 9 "is drawn to a genus i.e., a [sic] ***a single polypeptide*** comprising . . . " (emphasis in original).

Additionally, the Examiner cited *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997) and further stated:

> The only working examples are directed to polynucleotides encoding polypeptides comprising a DNA binding domain, and an ecdyson[e] ligand binding domain and polynucleotides encoding [a] transactivation domain and a mouse RXR or a chimeric RXR-USP ligand binding domain. There are no examples, working or prophetic, of polynucleotides encoding for example, chimeric polypeptides comprising an ecdysone ligand binding domain and a second ligand binding domain.
>
> Thus, the claims of the instant invention encompass numerous species that are not further described.
>
> In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genera, which are a ***single polynucleotide*** encoding a receptor complex comprising: A) a DNA binding domain; B) an ecdysone receptor ligand binding domain; C) a nuclear receptor ligand binding domain capable of forming a dimer with the ecdysone receptor ligand binding domain; and D) a

> transactivation domain and a ***single polypeptide*** comprising: A) a DNA binding domain; B) an ecdysone receptor ligand binding domain; C) a nuclear receptor ligand binding domain capable of forming a dimer with the ecdysone receptor ligand binding domain; and D) a transactivation domain.
>
> One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus.

Office Action at pages 12-13 (emphasis in original).

Applicants respectfully disagree. The claimed invention is described, and this conclusion is supported by Federal Circuit case law that has emerged since *Lilly* was published in 1997.

There is no bright line rule for determining whether or not a claimed genus is described. *See Ariad Pharmaceuticals, Inc. v. Eli Lilly and Company*, 598 F.3d 1336,1352 (Fed. Cir. 2010). That said, neither an actual reduction to practice nor examples are required to support a claimed genus. *See Ariad* at 1352 and 1358; and *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006).

It is not necessary for an application to disclose every permutation of a claimed invention in order to have described the invention. *See Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005). Instead, the level of disclosure required turns on the predictability of the technology. *See id.* at 1360 ("The predictability or unpredictability of the science is relevant to deciding how much experimental support is required to adequately describe the scope of an invention.").

Indeed, *less* disclosure is required for more predictable technologies. "The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge." *Id.* at 1358. *See also Ariad* at 1351; and

Billups-Rothenberg, Inc. v. Associated Regional And University Pathologists, Inc., 2011 U.S. App. LEXIS 8899 (Fed. Cir. 2011).

Moreover, the level of description needed to comply with the written description requirement:

> varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

Capon at 1357.

Structure can substitute for a representative number of species. *See In re Alonso*, 545 F.3d 1015, 1019 (Fed. Cir. 2008); see also *Invitrogen Corp. v. Clontech Labs, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005). However, recitation of *known* structure is not required. *See Falkner* at 1367 and *Invitrogen* at 1073.

At the June 1, 2011, Examiner interview, the Examiner asked if Applicants could provide a literature citation that would demonstrate that constructing a polynucleotide that encodes two or more polypeptides to be expressed in a cell was routine in the art at the time of filing the present application. Applicants submit as evidence a sampling of third-party publications (Exhibits A-D) demonstrating that this was, indeed, the case.

Applicants note that the publications submitted herewith were published between 1987 and 1996 (*i.e.*, about 4-13 years prior to the earliest priority application filing for the present application). Applicants also note that these publications represent but a small (but sufficient) sampling of the level of sophistication of the state of the art of

molecular cloning and gene/protein expression, prior to filing date of the present application.

Exhibit A is Kaufman *et al.*, "Translational Efficiency of Polycistronic mRNAs and their Utilization to Express Heterologous Genes in Mammalian Cells," *EMBO J. 6(1)*: 187-193 (1987), which demonstrates that as early as 1987, researchers were making and using vectors that encode multiple individual proteins from single polynucleotides. *See* Kaufman, *e.g.*, at the Abstract ("polycistronic expression vectors can be exploited to obtain high-level expression of foreign genes in mammalian cells"), and Figure 1 (depicting polycistronic elements in single plasmids, encoding ADA and DHFR (p9ADA5-29), CSF and DHFR (pCSF-1) and CSF, ADA and DHFR (p9CSF-ADA)).

Exhibit B is Ghattas *et al.*, "The Encephalomyocarditis Virus Internal Ribosome Entry Site Allows Efficient Coexpression of Two Genes from a Recombinant Provirus in Cultured Cells and Embyros," *Mol. Cell. Biol. 11(12)*: 5848-5849 (1991), which demonstrates that as early as 1991, researchers were making and using vectors that encode multiple individual proteins from single polynucleotides. *See* Ghattas, *e.g.*, at the Abstract and Figure 1 (disclosing that two different polypeptides -- LacZ and CAT -- could be efficiently expressed, *in vitro* and *in vivo*, from a single retroviral vector polynucleotide).

Exhibit C is Hofmann *et al.*, "Rapid Retroviral Delivery of Tetracycline-Inducible Genes in a Single Autoregulatory Cassette," *Proc. Nat. Acad. Sci. USA. 93*: 5185-5190 (1996), which demonstrates that as early as 1996 researchers were making and using vectors that encode and express multiple individual proteins from single

polynucleotides. *See* Hofmann, *e.g.*, at the Abstract and Figures 1 and 2 (showing that two different polypeptides -- LacZ and a Tet repressor-VP16 fusion protein -- can be efficiently expressed from a single polynucleotide (*i.e.*, from a single autoregulatory cassette) in mammalian cells (*e.g.*, primary mouse myoblasts)).

Exhibit D is Markowitz *et al.*, "A Safe Packaging Line for Gene Transfer: Separating Viral Genes on Two Different Plasmids," *J. Virology 62(4)*: 1120-1124 (1988), which shows that as early as 1988, researchers could also perform the *converse* of the above (Exhibits A-C), and *divide* gene coding sequences that naturally occur in a single vector (*i.e.*, viral *gag*, *pol*, and *env* genes) onto separate plasmids, and obtain complementary co-expression of such separated genes. *See* Markowitz, *e.g.*, at the Abstract and Figure 2 (disclosing construction of separate plasmids for complementary co-expression of the *gag*, *pol* and *env* genes)).

Hence, when the present application was filed, those of ordinary skill in the art knew how to make and use polynucleotide molecules encoding two or more polypeptides. Under *Falkner* and *Invitrogen*, that is enough to demonstrate that one of ordinary skill in the art would have understood that Applicants were in possession of the genus of polynucleotides recited in claim 1 and were in possession of the genus of polypeptides recited in claim 9. *See Falkner* at 1367 and *Invitrogen* at 1073.

In view of the amendments, arguments, and evidence provided herein and herewith, Applicants respectfully request that the outstanding rejections be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly addressed. Applicants therefore respectfully request that the Examiner reconsider and withdraw the presently outstanding rejections. Applicants believe that a full and complete reply has been made to the outstanding Office Action.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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